

In claim 33, at line 1 please delete "sequence".

In claim 34, at line 1, please delete "sequence".

02 38. (amended) A purified human 4-1BB polypeptide comprising the N-terminal amino acid sequence Leu-Gln-Asp-Pro-Cys-Ser-Asn-Cys-Pro-Ala-Gly-Thr-(amino acid residues 1-12 of SEQ ID NO:8), the polypeptide being capable of binding 4-1BB-L.

03 41. (amended) A purified soluble human 4-1BB polypeptide, wherein said polypeptide [comprises the extracellular domain of human 4-1BB)] is selected from the group consisting of polypeptides comprising amino acids 1-163 of SEQ ID NO:7(] or] and polypeptides comprising a fragment of amino acids 1-163 of SEQ ID NO:7, the fragment capable of binding a 4-1BB-L.

04 44. (amended) A [pharmaceutical] composition comprising [an effective amount of] a soluble human 4-1BB of claim 41 in admixture with a [suitable] diluent, carrier, or excipient.

REMARKS

In view of the foregoing amendment and the following remarks, Applicants respectfully request reconsideration of the claims pending in the present application. Claims 26, 27, 29-47 are pending in the application. Claims 29-44 and 47 are the subject of the present examination. Claim 29 is allowed and claims 30-44 and 47 stand rejected. In the Office Action mailed May 13, 1998 the examiner presented a requirement to restrict, noted sequence noncompliance and informalities, and rejected claims 30-44 under 35 U.S.C. §112, second paragraph and claims 38, 40, 44 and 47 under 35 U.S.C. §112, first paragraph. In the remarks that follow, Applicants discuss the restriction requirement, sequence issues, informalities, objections and rejections in the order in which they appear in the outstanding Office Action.

Applicant acknowledges the restriction requirement and the election to prosecution claims 29-44 and 47.

With respect to the Examiner's requirement to amend the sequence listing, Applicants have elected to delete the specific amino acids that are identified as the FLAG polypeptide (DYKDDDDK) from the specification. This peptide is well known and identified by its

tradename, FLAG. Thus, there is no requirement to recite the specific peptide sequence. With respect to the recitation of the N terminal amino acid in claim 38, the claim is amended to identify the sequence as amino acid residues 1-12 of SEQ ID NO:8. In view of the amendment to the specification and claim 38, the sequence listing is now in compliance with the sequence rules.

In response to the Examiner's request for a new title, Applicants have deleted the former title and provided a new title that is descriptive of human 4-1BB which is the subject matter of the claims. The Examiner also requested that the Summary of the Invention and the descriptive matter be restricted to describing only 4-1BB. It is Applicants' opinion that the summary of the invention and the disclosure are not extraneous to the claimed subject matter. The disclosure describes a ligand and receptor to which the ligand binds. Because the described molecules are binding partners, they are sufficiently related to make restriction of the disclosed subject matter unnecessary. Thus, Applicants request that the Examiner withdraw the requirement to rewrite the descriptive matter.

Turning to the Section 112 rejections, the Examiner first rejected claims 30-44 under 35 U.S.C. §112, second paragraph, as being indefinite. More particularly, in claims 30 and 41 the Examiner asserts that the claims are indefinite for the use of parentheses surrounding the phrase "amino acids . . ." In view of the above amendment in which claims 30 and 41 are amended to remove the parentheses and clarify language, Applicants submit that amended claims 30 and 41 are not indefinite and request that this rejection be withdrawn.

The Examiner additionally rejected claims 32-34 as being indefinite because there is no antecedent basis in claims 29-31 for "a DNA sequence". Since amended claims 32-34 do not contain the term "sequence", there is proper antecedent basis and this rejection should be withdrawn.

In another Section 112 rejection the Examiner asserted that claim 38 is indefinite because the Examiner is of the opinion that the metes and bounds of a "human 4-1BB" polypeptide cannot be determined. More particularly, the Examiner asserts that it cannot be determined whether claim 38 is intended to be limited to full-length, naturally occurring human 4-1BB, or is intended to encompass fragments and derivatives of such. Applicants submit that claim 38, as amended, recites human 4-1BB polypeptides that have the recited N-terminal amino acid residues *and* which are capable of binding 4-1BB-L. Since the scope of the present invention includes variants, fragments, derivatives and naturally occurring 4-1BB polypeptides, and since the law does not require a claim to encompass a single embodiment,

and claim 38 is clear in its language, Applicant submits that claim 38 is not indefinite and requests that this rejection be withdrawn.

The Examiner additionally rejected claim 40 as being indefinite because the Examiner is of the opinion that the claim allows an unspecified number of conservative amino acid substitutions and it is not clear how many such substitutions may be made. Applicants respectfully argue that claim 40 is definite in that conservative amino acid substitutions for each amino acid is well known in the art. Since the amino acid sequence is known all possible conservative substitutions are known. It is also known in the art that such substitutions can be made without significantly compromising the polypeptide activity. Furthermore, there is no requirement that the number of specific substitutions be recited in the claims. Since the specific sequences available for conservative substitutions are recited in the claims and each conservative amino acid substitution is known, sequences encompassed by the claims are clearly defined. Thus, claim 40 is not ambiguous or indefinite and this rejection should be withdrawn.

With respect to claim 41 and the Examiner's opinion that the term "capable of binding a 4-1BB-L" renders the claim indefinite, Applicants respectfully traverse the Examiner's rejection. The Examiner appears to be of the opinion that the language "capable of binding" is inconsistent with a positive recitation of binding. Applicants submit that the term "capable of binding" is clear and unambiguous in that it positively recites that the claim fragment is able to bind 4-1BB-L. In the absence of a 4-1BB-L, the capability is present, but the binding does not occur. Applicants request that the Examiner clarify the position that the term "capable of binding" renders claim 41 indefinite. As for the Examiner's assertion that it is not clear whether applicants intend a naturally occurring 4-1BB-L or any moiety that binds to 4-1BB, Applicants submit that the specification very clearly describes the scope of 4-1BB-L. The specification describes naturally occurring 4-1BB-L DNA and amino acid sequences and 4-1BB-L fragments, derivatives and mutants, all of which are 4-1BB-L molecules. Since the specification is clear in its description of 4-1BB-L, the Examiner's position that claim 41's recitation of 4-1BB-L molecules is indefinite is in error and the rejection should be withdrawn.

In another Section 112, second paragraph, rejection, the Examiner rejected claim 44 as being indefinite. Claim 44 recites the language "effective" amount of . . . with a "suitable" diluent and the Examiner's position is that it cannot be determined what amount would be "effective", nor what type of diluent would be "suitable." By the above amendment, Applicants have deleted the term "effective". With respect to the term "suitable", Applicants

submit that the specification provides clear description of those diluents, carriers or excipients considered suitable. For example, on page 19 beginning at line 14, the specification describes compositions and the class of diluents, excipients and carriers that are suitable. Notwithstanding this, by the above amendment, Applicants have deleted the term "suitable" from claim 44. In view of the recitation of amended claim 44, this claim is not indefinite and this rejection should be withdrawn.

Finally, the Examiner rejected claims 31, 35-37, 39, 42 and 43 as depending from an indefinite claims. Applicants submit that in view of the above amendment and remarks, the claims from which claims 31, 35-37, 39 42 and 43 are not indefinite. Thus, claims 31, 35-37, 39, 42 and 43 are not dependent upon indefinite claims and this rejection should be withdrawn.

The Examiner next rejected claims 38, 40, 44 and 47 under 35 U.S.C. §112, first paragraph, because the Examiner is of the opinion that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with the claims. With respect to claim 38, the Examiner states that the claim encompasses all possible variants of 4-1BB which have the recited N-terminal sequence. According to the Examiner the specification does not teach how to use a commensurate number of such species which do not retain the ability to bind 4-1BB-L and it would require undue experimentation to determine how to use the species which do not retain such binding function. Since amended claim 38 now recites a functional limitation in addition to sequence information, this claim does not encompass all possible variants of 4-1BB having the recited N-terminal sequence. The scope of amended claim 38 includes 4-1BB molecules having the recited N-terminal sequence *and* the recited ability to bind 4-1BB-L. Testing polypeptides having the recited N-terminal amino acid sequence for the ability to bind 4-1BB-L can be accomplished using conventional binding assays that are well known in the pertinent field, some of which are disclosed in the specification on page 12 and examples 5 and 6. Thus, the teachings of the present specification, taken in combination with the knowledge available in the pertinent field enables the skilled artisan to prepare polypeptides having the recited N-terminal amino acids, to determine whether a given variant binds 4-1BB-L, and use the claimed polypeptide. Accordingly, claim 38 is allowable and the rejection should be withdrawn.

With respect to claim 40, the Examiner similarly argues that this claim allows conservative substitutions in the protein of SEQ ID NO:7, but the claim specifies no function. The Examiner states that while the person of ordinary skill in the art would be able to make

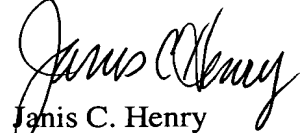
such species, the specification does not teach how to use any such species which does not retain the ability to bind to 4-1BB-L. Since claim 40 recites the polypeptide of claim 38 with the additional limitations, and polypeptides of amended claim 38 are capable of binding 4-1BB-L, claim 40 does recite polypeptides that have the ability to bind 4-1BB-L. As the Examiner mentions and as described above, the specification is enabling for polypeptides that bind 4-1BB-L having the specified amino acid sequences or the specified sequences that are conservatively substituted. Accordingly, this rejection is overcome and should be withdrawn.

The Examiner also rejected claim 44 because the Examiner believes that the specification does not enable pharmaceutical compositions that include 4-1BB. Since amended claim 44 no longer recites pharmaceutical compositions and the specification describes uses of 4-1BB that include reagents in protein purification processes and 4-1BB-L binding assays, the specification enables compositions as recited in amended claim 44. Thus, the Examiner's rejection of claim 44 is overcome and should be withdrawn.

Finally, the Examiner rejected claim 47 as been nonenabled. The Examiner believes that enablement is commensurate in scope with fragments of at least about 17 nucleotides of the DNA of claim 29, but not commensurate in scope with all fragments of degenerate variants of SEQ ID NO:7. The Examiner's position is that the specification does not teach how to use fragments because they are generally considered to be useful as hybridization probes or primers, but large numbers of claimed degenerate variants would not hybridize to naturally occurring 4-1BB sequences. The Examiner further believes that the degenerate fragments would not encode an antigenic portion of the disclosed protein. Applicants respectfully disagree with the Examiner's position. With respect to their use as probes, a large number of degenerate variants will hybridize to 4-1BB. Enablement does not require that all embodiments encompassed by a claim need be operative for all disclosed uses as long as operative embodiments can be determined without undue experimentation. Since, it is within the skill and knowledge of one ordinarily skilled in the art to determine which probes hybridize to any given nucleotide sequence, degenerate fragments are fully enabled. With respect to degenerate fragments that encode peptides having antigenic utility, Applicants assert that it is well within the knowledge of those ordinarily skilled in the art to determine which encoded peptides have utility as epitopes. Again, since enablement does not require that all embodiments encompassed by a claim need be operative as long as operative embodiments can be determined, claim 47 is enabled and this rejection should be withdrawn.

In view of the foregoing amendment and remarks, Applicants respectfully submit that the claims pending in this application are now in condition for allowance and a notice to that effect is respectfully requested.

Respectfully submitted,



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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: BOX NON FEE, Assistant Commissioner for Patents, Washington, D.C. 20231, on the date indicated below.

Date: August 13, 1998

Signed: 